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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/755,082	01/09/2004	Brian Dalby	IVGN 349	8189

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/755,082	DALBY ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-117* is/are pending in the application.

4a) Of the above claim(s) *1-60 and 91-117* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *61-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Attachments

DETAILED ACTION

An amendment was received and entered on 10/12/06. Applicant's election with traverse of Group 5, claims 61-90 is acknowledged. Traversal is on the grounds that a search of Group 5 would be substantially coextensive with a search of groups 1-4 and 6-8, and would necessarily lead to art that was relevant to these groups. This is unpersuasive because it is only a statement of belief and is not supported by evidence or reasoning. The restriction requirement properly showed that the various methods compositions and kits were patentably distinct for the reasons of record. The requirement is still deemed proper and is therefore made FINAL. Claims 1-60 and 90-117 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/12/06.

Specification

The specification is objected to because the pages are not properly numbered. The specification begins with pages 1-46, after which occur pages numbered 44-48, and then 53-157. Appropriate renumbering is required.

Information Disclosure Statement

The information disclosure statement filed 12/5/05 lists document 192, 2000/12660 A1, but lists no publication date or inventor. As far as the Examiner can tell, there is no such document, and reference 192 was not considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 61-90 are drawn to the genus of treatments that result in dissociation of a nucleic acid from a fluorescent molecule and/or a cellular delivery vehicle. The only such treatment disclosed in the specification is electromagnetic radiation (see e.g. paragraph 24). The claims recite no nexus between any treatment and any element of the nucleic acid complex, such as a fluorophore, and require no functional relationship between any treatment and any specific element of the nucleic acid-containing complex. On the other hand, the prior art taught that the release of nucleic acids from delivery complexes comprising fluorophores was dependent on exposing the fluorophore to

electromagnetic radiation of an excitatory wavelength. See e.g. Normand, N., et al., J. Biol. Chem. 276:15042-15050 (2001), of record, discussed at page 2 of the specification. In view of the failure of the specification to provide any example or description of any treatment that results in dissociation of a nucleic acid from a fluorescent molecule and/or a cellular delivery vehicle, other than electromagnetic radiation, and in view of the fact that the claims require no type of relationship at all between the treatment and any element of the nucleic acid complex, one of skill in the art could not conclude that Applicant was in possession of the claimed genus of treatments at the time the application was filed.

Claims 73, 83, and 84 are drawn to the genus of cellular delivery polypeptides that have an amino acid sequence that is not present in the amino acid sequence of a protein encoded by herpes simplex virus. The genus of proteins encoded by herpes simplex viruses is constantly changing as these viruses evolve through mutation. As a result one of skill in the art cannot know what are the metes and bonds of the genus, and Applicant could not have been in possession of this genus at the time of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 61, 63-75, and 80-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Curiel et al (US 5547932).

Curiel taught methods of delivering nucleic acids or oligonucleotides to cells, wherein the nucleic acids or oligonucleotides are complexed to a conjugate of polylysine and transferrin. Transferrin induces receptor-mediated uptake into the endosome-lysosome pathway. Nucleic acid release from endosomes/lysosomes, and from the complex is facilitated by addition of chloroquine or an adenovirus. See entire document, e.g. paragraph bridging columns 4 and 5, and Examples 6, 9, 15, 16, 22, 23, and 38. Transferrin can be considered to be the fluorescent molecule as it comprises many aromatic amino acids. Either transferrin or polylysine can be considered to be a cellular delivery molecule. Regarding claim 68, all nucleic acids are considered to be chemically modified as their synthesis requires the stepwise addition of nucleotides onto a growing chain of nucleotides. Regarding claim 72, the limitation "synthetic peptide" is considered to be met by either transferrin or polylysine. The term "synthetic" receives no weight because it is a product by process limitation that does not affect the structure or function of the peptide. The term "peptide" is interpreted broadly to embrace any molecule linking two or more amino acids by a peptide bond. The polylysine of Curiel is considered to be the cellular delivery peptide of claims 73, 83, and 84. The reference is considered to anticipate claims 74 and 75 a few different ways. In one interpretation, the polylysine and the transferrin can be considered to be a fusion protein because they are each proteins that are fused to each other covalently, if not by a peptide bond. In another interpretation, any portion of polylysine of transferrin can be considered to be

fused to any other part of polylysine or transferrin, respectively, i.e. the first five residues of polylysine can be considered to form a fusion protein wit the remaining polylysine residues. Regarding claim 87, any fluorescent portion of transferrin can be considered to be fused to any other portion of transferrin, or to polylysine. Regarding claim 88, any of the polylysine, transferrin, chloroquine, or adenovirus can be considered to be a transfection agent.

Claims 61-68, 70-75, 80, and 83-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Normand et al. (J. Biol. Chem. 276:15042-15050 (2001)), as evidenced by GenBank Accession No. BAE87004, 3/17/06 and http://www.clinalfa.com/docs/docs/PROT/TB070.pdf.

Normand taught a method of delivering to cells a complex of a VP22 fusion protein and fluorescein labeled antisense oligonucleotides, and illuminating the cells with an excitatory wavelength of light in order to dissociate the oligonucleotides from the fusion protein. See entire document, especially abstract, and page 15044 column 2, first full paragraph to page 15046, column 1, line 4. The sequence of the VP22 fusion protein was deduced from page 15043, column 1, second full paragraph of Normand, in combination with GenBank Accession No. BAE87004, and manufacturer information for the expression vectors pET24a-d found at http://www.clinalfa.com/docs/docs/PROT/TB070.pdf. The protein comprises 14 N-terminal amino acids derived from pET24b, as well as a C-terminal 6-H His-tag. Regarding claims 73, 83, and 84, the pI of this peptide was

calculated by the Examiner to be 11.8, using the EMBL WWW Gateway to Isoelectric Point Service at http://www.embl-heidelberg.de/cgi/pi-wrapper.pl. See attachments.

Regarding claim 73, item b, the fusion protein comprises 6 consecutive H residues (i.e. the His-Tag). Regarding claim 73, item c, the fusion protein contains 14 N-terminal amino acids derived from the vector and not VP22, as well as the 6 consecutive H residues mentioned above.

Regarding claim 80, the oligonucleotides of Normand are considered to encode a portion of a protein because they contain codons.

Regarding claims 85-87, the VP22 fusion peptide is considered to be fluorescent because it has a variety of aromatic residues.

Claims 61-75 and 80-90 are rejected under 35 U.S.C. 102(a) and 102 (e) as being anticipated by Berg et al (US 20020155099).

Berg taught methods of photochemical internalization of nucleic acids. Nucleic acids are complexed with vectors, such as antibodies or polylysine, that direct cellular uptake, and contacted to cells resulting in uptake into the endosome-lysosome pathway. Cells are also contacted with a fluorescent photosensitizer, which may be attached to the delivery vector, and are finally subjected to illumination resulting in release of the nucleic acids from endosomes/lysosomes. See entire document, especially abstract and paragraphs 8-10, 43, 49. Note that Berg also taught delivery to cells of fluorescein-labeled oligonucleotides and subsequent detection of the fluorescein by illumination, exactly as taught by Normand above. See Berg at paragraphs 102-111.

Regarding claim 72, the limitation "synthetic peptide" is considered to be met by either antibodies or polylysine. The term "synthetic" receives no weight because it is a product by process limitation that does not affect the structure or function of the peptide. The term "peptide" is interpreted broadly to embrace any molecule linking two or more amino acids by a peptide bond. The polylysine of Berg is considered to be the cellular delivery peptide of claims 73, 83, and 84. The reference is considered to anticipate claims 74 and 75 because any portion of polylysine can be considered to be fused to any other part of polylysine (i.e. the first five residues of polylysine can be considered to form a fusion protein with the remaining polylysine residues). Either of these portions can be considered to be an "accessory" as required by claim 75. Regarding claims 85-87, absent evidence to the contrary polylysine and antibodies are fluorescent, and any fluorescent portion of them can be considered to be fused to any of their other portions. Regarding claim 88, any of the polylysine, antibody, and photosensitizer can be considered to be transfection agents.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 61, 71, and 74-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wahl (US 5654182) in view of with either one of Curiel (US 5547932) or Berg et al (US 20020155099).

Wahl taught a method for the integration of a first nucleic acid into the genome of a mammalian host cell, said method comprising stably integrating a first FLP recombination target site (FRT) into-said genome; and introducing into said mammalian host cell of step a) an FLP recombinase and said first nucleic acid, wherein said first nucleic acid comprises a second FRT, and wherein said FLP recombinase catalyzes recombination between said first FRT and said second FRT, thereby precisely targeting integration of said first nucleic acid into said genome at the site of said first FRT.

Wahl did not teach contacting the cell with a fluorescent molecule, a cellular delivery molecule, or treating the cell with a treatment that results in dissociation from the nucleic acid of either the fluorescent molecule or the cellular delivery molecule.

Curiel taught methods of delivering nucleic acids, wherein the nucleic acids are complexed to a conjugate of polylysine and transferrin. Transferrin induces receptor-mediated uptake into the endosome-lysosome pathway. Nucleic acid release from endosomes/lysosomes, and from the complex is facilitated by addition of chloroquine or an adenovirus. See entire document, e.g. paragraph bridging columns 4 and 5, and Examples 6, 9, 15, 16, 22, 23, and 38.

Berg taught methods of photochemical internalization of nucleic acids. Nucleic acids are complexed with vectors, such as antibodies or polylysine, that direct cellular uptake, and contacted to cells resulting in uptake into the endosome-lysosome pathway.

Cells are also contacted with a fluorescent photosensitizer, which may be attached to the delivery vector, and are finally subjected to illumination resulting in release of the nucleic acids from endosomes/lysosomes. See entire document, especially abstract and paragraphs 8-10, 43, 49. Note that Berg also taught delivery to cells of fluorescein-labeled oligonucleotides and subsequent detection of the fluorescein by illumination, exactly as taught by Normand above. See Berg at paragraphs 102-111.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the nucleic acid of Wahl using the method of Curiel. One would have been motivated to do so because the method of Curiel is a receptor-mediated endocytosis method that has major advantages (non-toxic mechanism of passage through the cell membrane; the possibility of administering biologically active nucleic acids, such as nucleic acids which specifically inhibit genes, or cellular functions, on a repeated or continuous basis; the possibility of cell-specific targeting; the possibility of producing the conjugates in large quantities). See column 4, lines 50-59. Note that Wahl envisions adding the recombinase simultaneously with the nucleic acid to be delivered. Note also that the recombinase of Wahl can be considered to be a cellular delivery polypeptide inasmuch as it catalyzes the delivery of a nucleic acid into the genome of a cell. The recombinase can also be considered to be a fusion protein, i.e. the N-terminal half of the recombinase is fused to the C-terminal half.

It would have been similarly obvious to use the method of Berg to deliver the nucleic acids of Wahl, and one would have been motivated to do so because the

method of Berg facilitates release from endosomes, thereby limiting the amount of transfecting nucleic acid lost to lysosomal degradation.

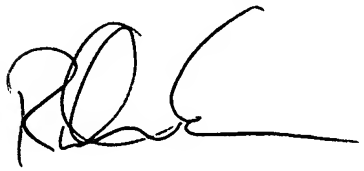
Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635

SEARCH NOTES

S26515	U	PGPB,USPT,EPAB,DWPI	Berg.in. and tpps$ and (polycation$ or polylysine or poly lysine or poly l lysine) and (antibody or ligand or target$)	2006-11-20 12:19:53
S26514	U	PGPB,USPT,EPAB,DWPI	(5654182 or 5547932).pn.	2006-11-20 11:54:05
S26513	U	PGPB,USPT,EPAB,DWPI	(5654182 or 6680301).pn.	2006-11-20 11:50:42
S26512	U	PGPB,USPT,EPAB,DWPI	Berg.in. and tpps$ and (polycation$ or polylysine or poly lysine or poly l lysine)	2006-11-20 11:47:19
S26511	U	PGPB,USPT,EPAB,DWPI	Berg.in. and tpps$	2006-11-20 11:40:53
S26510	U	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	Berg.in. and tpps	2006-11-20 11:40:17
S26509	U	PGPB,USPT	(5547932 or 5981273 or 6022735 or 6077663 or 6274322).pn. and (lipid or liposome or lipfect$)	2006-11-20 09:07:17
S26508	U	PGPB,USPT	(5547932 or 5981273 or 6022735 or 6077663 or 6274322).pn. and chloroquine	2006-11-20 08:35:39
S26507	U	PGPB,USPT	(5547932 or 5981273 or 6022735 or 6077663 or 6274322).pn. and	2006-11-20 08:20:42

		oligonucleotide and (polylysine or poly lysine or poly l lysine or polycation$)	
S26506	U PGPB,USPT	(5547932 or 5981273 or 6022735 or 6077663 or 6274322).pn. and oligonucleotide	2006-11-20 08:18:46
S26505	U PGPB,USPT	((wagner and cotten and birnstiel).in. and (polylysine or poly lysine or poly l lysine or polycation$) and chloroquine) and oligonucleotide	2006-11-20 08:16:55
S26504	U PGPB,USPT	5547932.pn. and oligonucleotide	2006-11-20 08:15:51
S26503	U PGPB,USPT	(wagner and cotten and birnstiel).in. and (polylysine or poly lysine or poly l lysine or polycation$) and chloroquine	2006-11-20 07:18:01
S26502	U USPT	(transferrinfection or transferinfection) and (wagner.in.) and chloroquine and fusion protein	2006-11-20 07:13:58
S26501	U USPT	(transferrinfection or transferinfection) and (wagner.in.) and chloroquine and fusion	2006-11-20 07:13:46
S26500	U USPT	(transferrinfection or transferinfection) and (wagner.in.)	2006-11-20 07:09:48

		and chloroquine	
S26499	U USPT	(transferrinfection or transferinfection) and (wagner.in.)	2006-11-20 07:09:27
S26498	U USPT	transferrinfection or transferinfection	2006-11-20 07:09:05
S26497	U PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	berg.in. and tpps$ and (polylysine or poly lysine or poly l lysine or polycation$)	2006-11-20 07:00:45
S26496	U USPT	berg.in. and tpps$	2006-11-20 06:59:28
S26495	U USPT	(CRE OR LOX or flp or frt).clm. and recombinase.clm.	2006-11-20 06:53:06
S26494	U USPT	((CRE OR LOX or flp or frt).clm. and recombinase.clm.)	2006-11-20 06:52:59
S26493	U PGPB	((CRE OR LOX or flp or frt).clm. and recombinase.clm.)	2006-11-20 06:52:53